Research Report

Comparison of Macrophage Migration-Inhibitory-Factor (MIF) Serum Level between 28 - 36 Weeks of Pregnancy and Delivery

Perbandingan Kadar Serum Macrophage Migration Inhibitory Factor antara Kehamilan dan Persalinan 28 - 36 Minggu

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Abstract

Objective: To analyze the differences in Macrophage Migration Inhibitory Factor (MIF) serum level between 28 - 36 weeks of pregnancy and delivery, and determine the serum level of Macrophage MIF as a risk factor for preterm labor.

Methods: The design of our study was cross sectional of 72 subjects who met the inclusion- and exclusion-criteria that came to Dr. Hasan Sadikin Hospital, Bandung and six satelite hospitals (in July-August 2011). Macrophage Migration Inhibitory Factor (MIF) level was measured with ELISA. Comparison of mean serum levels of MIF between 28 - 36 weeks of pregnancy and delivery was analyzed using the Mann Whitney test. MIF level, which is a risk factor for preterm delivery, was calculate with a prevalence ratio (PR) based on ROC curve.

Results: Characteristics test in both groups showed homogeneous and comparable data. The mean levels of Macrophage Migration Inhibitory Factor (MIF) in 28 - 36 weeks of delivery was higher (54.433 ng/ml) compared with 28 - 36 weeks of gestation (31.765 ng/ml) with $p \leq 0.001$. MIF levels > 37.684 ng/ml had a risk for preterm labor incidence 3.35 times greater than that of ≤ 37.684 ng/ml.

Conclusion: Serum levels of Macrophage Migration Inhibitory Factor (MIF) at delivery was higher than that of at 28 - 36 weeks pregnancy. MIF levels > 37.684 is a risk factor for preterm labor.

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Keywords: Macrophage Migration-Inhibitory-Factor (MIF), preterm labor

Abstrak

***Tujuan**: Penelitian ini adalah menganalisis perbedaan kadar serum Magrophage Migration Inhibitory Factor (MIF) antara kehamilan dan persalinan 28 - 36 minggu dan menganalisis kadar serum Magrophage Migration Inhibitory Factor (MIF) yang merupakan faktor risiko kejadian persalinan kurang bulan.*

***Metode**: Rancangan penelitian ini adalah potong silang (cross sectional) terhadap 72 subjek penelitian yang memenuhi kriteria inklusi dan eksklusi yang datang ke RS Dr. Hasan Sadikin Bandung dan enam rumah sakit jejaring periode Juli - Agustus 2011. Kadar serum MIF diperiksa dengan ELIZA. Perbandingan rerata kadar serum Macrophage Migration Inhibitory Factor (MIF) antara kehamilan dan persalinan 28 - 36 minggu menggunakan uji Mann Whitney, dan kadar MIF yang merupakan penentu persalinan kurang bulan dihitung dengan ratio prevalen (PR) berdasarkan kurva ROC.*

***Hasil**: Uji karakteristik pada kedua kelompok penelitian menunjukkan kedua kelompok homogen dan dapat diperbandingkan. Rerata kadar Macrophage Migration Inhibitory Factor (MIF) pada persalinan 28-36 minggu lebih tinggi (54,433 ng/ml) dibandingkan dengan kehamilan 28-36 minggu (31,765 ng/ml) ($p \leq 0,001$). Kadar MIF > 37,684 ng/ml mempunyai risiko kejadian persalinan kurang bulan 3,35 kali lebih besar dibandingkan kadar MIF ≤ 37,684 ng/ml.*

***Kesimpulan**: Kadar serum Macrophage Migration Inhibitory Factor (MIF) pada persalinan lebih tinggi dari kehamilan 28 - 36 minggu. Kadar MIF > 37,684 merupakan faktor risiko kejadian persalinan kurang bulan.*

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***Kata kunci**: Macrophage Migration Inhibitory Factor (MIF), persalinan kurang bulan*

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INTRODUCTION

Preterm labor is still a problem in obstetrics and perinatology since it deals with high rates of infant morbidity and mortality. The incidence of preterm labor is ± 7 - 8% of all deliveries contributing ± 85% in perinatal deaths.[1]

In developing countries the number of events was much higher, which were, around 30% in India, 15% in South Africa, 31% in Sudan, and 10% in Malaysia.[2] Alisjahbana et al, reported the incidence of preterm labor in Dr. Hasan Sadikin Hospital (RSHS) Bandung to be 17.4%.[3] The annual report of Obstetrics and Gynecology RSHS Bandung, obtain a number of 18% preterm labor from all deliveries and it has not changed over the last 10 years.[4]

According to Green et al, more than 60% of preterm labor cannot be explained, it is generally only described as idiopathic preterm labor and premature rupture of membranes. Some experts argue that these two things are associated with subclinical inflammatory response in fetal and maternal tissues.[5]

The mechanism of preterm labor is still being debated. Lockwood et al., stated that there were four mechanisms that may lead to preterm labor; Activation of the hypothalamic-pituitary-adrenal axis (HPA) of the fetus and the mother, systemic inflammation or inflammation on decidua and chorioamnion, decidual hemorrhage, pathologic uterine distension such as multiple pregnancy, polyhydramnios, and uterine abnormalities.[6] Several studies have been conducted to predict the occurrence of preterm labor.[7] Currently,

many studies are focused on targeting bio-chemical markers of preterm labor analyzing a variety of cytokines and extracellular matrix of fetal membranes, cytotrophoblasts, decidua or cervix.

One of the proinflammatory cytokine, MIF, is contributing to initiation of preterm labor. MIF is a potent cytokine, that can be produced by various cell types and normal tissue, macrophage, monocytes, endocrine, and the reproductive organs. MIF is considered as a major mediator in the inflammatory response. Recent studies have shown that MIF is a cytokine that plays a role in maintaining pregnancy.[8] MIF induces the synthesis of other pro-inflammatory mediators such as TNF-α, IL-1, IL-6, IL-8 and has a unique ability to inhibit steroid suppression on cytokine synthesis. Moreover MIF is a potent activator of macrophages, which induces various biological functions of these cells such as adhesion, phagocytosis, intracellular parasite eradication and introduction of nitric oxide production.[8]

Up to now, few studies have been done to find-out the relationship between MIF and preterm labor. Pearce et al, stated that levels of MIF measured in trimesters I and II could used to predict the incidence of premature labor, with a cut-off point of 9.16 ng/ml.[9]

METHOD

Our study design was cross sectional of seventy-two patients who met the inclusion- and exclusion-criteria that came to our outpatient clinic at Dr. Hasan Sadikin Hospital Bandung and six satelite hospital between July and August 2011. Comparison of the mean serum levels of MIF between 28 - 36 weeks of pregnancy and delivery was analyzed using the Mann Whitney test. MIF level, which is risk factor for preterm delivery, was calculated with a prevalence ratio (PR) based on ROC curve.

RESULTS

Serum levels of MIF in 28 - 36 weeks of pregnancy and delivery were obtained with a cross-sectional study of 72 patients who met the inclusion- and exclusion-criteria.

Table 1 showed that there was no difference in the characteristics of patients based on age, parity, gestational age, and asymptomatic bacteriuria between 28 - 36 weeks of pregnancy and delivery with p value of 0.691, 0.222, 0.616, 0.301, 1.0, respectively. Therefore, both groups were comparable.

Table 2. Comparison of serum levels of Macrophage Migration Inhibitory Factor (MIF) between mothers 28-36 weeks of pregnancy and delivery.

Variable	Research Group		p value*)
	28 - 36 Weeks Delivery (n=36)	28 - 36 Weeks Pregnancy (n=36)	
MIF Level's			< 0.001
Mean(±SD)	54.433 (25.797)	31.765 (9.654)	
Median	48.026	29.500	
Range	21.199 - 119.796	19.708 - 58.820	

*) *Mann Whitney test*

Table 1. Characteristics of patients.

Characteristics	Research Group				p value*)
	28 - 36 Weeks Delivery (n = 36)		28 - 36 Weeks Pregnancy (n = 36)		
	N	%	N	%	
Age (year)					0.691
< 20	4	11.1	2	5.6	
20 - 35	27	75.0	29	80.6	
> 35	5	13.9	5	13.9	
Parity					0.222
P 0	13	36.1	10	27.8	
P 1 - 3	19	52.8	25	69.4	
P ≥ 4	4	11.1	1	2.8	
Gestational Age (Weeks)					0.616
28 - 30	11	30.6	15	41.7	
31 - 33	11	30.6	9	25.0	
34 - 36	14	38.9	12	33.3	
Bacteriuria					0.306
Positif	9	25.0	13	36.1	
Negatif	27	75.0	23	63.9	
Stress					1.0**)
Yes	4	11.1	3	8.3	
No	32	88.9	33	91.7	

*) *Chi Square test*
**) *Fisher's exact test*

Table 3. Serum levels of Macrophage MIF based on ROC curve (Receiver Operating Characteristics) between 28 - 36 weeks pregnancy and delivery.

Variable	Research Group				p value*)	PR (95%CI)
	28 - 36 Weeks Delivery (n = 36)		28 - 36 Weeks Pregnancy (n = 36)			
	N	%	N	%		
MIF Level's					< 0.001	3.35 (1.85 - 6.08)
> 37.684	27	75.0	7	19.4		
≤ 37.684	9	25.0	29	80.6		

*) *Chi Square test*

Table 2 showed that there were significantly different levels of serum Macrophage MIF between 28 - 36 weeks of pregnancy and delivery with p value of $p < 0.001$.

According to ROC curve (receiver operating characteristics), cut-off point serum level of Magrophage Migration Inhibitory Factor (MIF) in 28 - 36 weeks of delivery was > 37.684 ng/ml With an area under the ROC curve being 0.806 showing a good validity.

Table 3 showed that the prevalence ratio value (PR) of Macrophage MIF serum of 28 - 36 weeks delivery was 3.35, which indicated that Macrophage MIF levels > 37.684 had 3.35 times risk for preterm labor. Validity test on the serum Macrophage MIF of 28 - 36 weeks delivery showed a sensitivity of 75.0%, specificity 80.6%, 79.4% positive expected value, 76.3% negative expected value, and an accuracy of 77.8% at a cut-off point of 37.684.

DISCUSSION

Characteristics of Research Subjects

From epidemiological point of view, there are several risk factors for preterm labor, which are:[10-2] Idiopathic, factors, iatrogenic, factors Infections (both extra- and intra-uterine), Maternal factors (maternal disease, cervical incompetence, and stress), reproductive history (a history of previous prematurity, primiparity, parity, short interval of two pregnancies, low maternal weight during pregnancy), sociodemographic (low socioeconomic status, age is too young or too old, race, marital status, unfavorable environmental factors, heavy physical activities).

Maternal age that is too young or too old is a risk factor for preterm labor. A study in Sweden stated that pregnant women with an age between 13 - 17 years and more than 35 years have an increases risk of preterm labor two times the control group of women aging 20 - 30 years.[12]

Preterm labor is more common in the first pregnancies. Incidence will be reduced by increasing the number of parity sufficient months to the fourth parity.[12] The incidence of asymptomatic bacteriuria urine was approximately 2 - 7% of all pregnancy.[13] According to Sheiner et al, of 199.093 deliveries; 2.5% (4890) of patients experienced asymptomatic bacteriuria, with E.Colli as the most isolated bacteria.[14] Moutquin et al, proved that stress associated with an incidence of prematurity consisted of events of death, domestic violence and financial problems.[15]

In our study, both treatment groups were homogeneous for age, parity, gestational age, asymptomatic bacteriuria and stress between 28 - 36 weeks of pregnancy and delivery, thus reasonable so worthy to be compared.

Comparison of Macrophage Migration Inhibitory Factor Serum Levels between 28 - 36 Weeks Pregnancy and Delivery

Serum levels of MIF increased among pregnant women than non-pregnant women, but there was no significant change in MIF levels between the first trimester of pregnancy, the second and the third.[16]

According Ietta et al, serum levels of MIF did not change with increasing gestational age median of 4.32 ng/ml, interval 0.60 - 21.33 for gestation of preterm labor.[8]

According Chaiworapongsa et al, there was no difference in plasma MIF levels among patients with preterm contractions and intact membranes, preterm and full term delivery (full term delivery; n = 18), median 52 ng/ml, interval 24-152; preterm labor, n = 27), median 55 ng/ml, range 13-160).[17]

According to Pearce et al, there were differences in MIF serum levels among women who gave birth full term and prematurely when measured in at 9 - 23 weeks of gestation with a median of 9.22 ng/ml (6.22 - 12.06) for women who premature delivery and a median of 7.00 ng/ml (5.64 - 9.17) for the full termed.[9]

This study indicated that there were different levels of serum MIF between 28 - 36 weeks of pregnancy and delivery.

Analysis of MIF Level as a Risk Factor for Preterm Labor

Some types of infection associated with preterm labor include: urinary tract infections, cervicitis, bacterial vaginosis, trichomoniasis and several others, such as candida vaginal, group B streptococcus, N gonorrhoeae, U urealyticum.[18-20]

Research on types of work and physical activities stated that conditions of stress, and hard work in the long hours were associated with preterm birth.[6] According to Pearce et al, increased MIF is associated with a diagnosis of bacterial vaginosis (BV) in early pregnancy.[9]

In this study we obtained prevalence ratio (PR) of 3.35 which indicates that when levels of Macrophage MIF is > 37.684 ng/ml the risk for preterm delivery

becomes 3.35 times greater than if levels of migration inhibitory factor Macrophage (MIF) is lower at ≤ 37.684 ng/ml.

CONCLUSION

The mean levels of MIF in deliveries that happen in 28 - 36 weeks of gestational age are higher compared with 28 - 36 of weeks pregnancy. Level of Macrophage Migration Inhibitory Factor (MIF) > 37.684 is a risk factor for preterm labor increasing incidence by 3.35 times compared to level of MIF ≤ 37.684.

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